Prevalence of PALB2 Germline Mutations in Early-onset and Familial Breast/Ovarian Cancer Patients from Pakistan

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Purpose
Partner and localizer of BRCA2 (PALB2) is a breast cancer susceptibility gene that plays an important role in DNA repair. This is the first study assessing the prevalence of PALB2 mutations in early-onset and familial breast/ovarian cancer patients from Pakistan.

Materials and Methods
PALB2 mutation screening was performed in 370 Pakistani patients with early-onset and familial breast/ovarian cancer, who were negative for BRCA1, BRCA2, TP53, CHEK2, and RAD51C mutations, using denaturing high-performance liquid chromatography analysis. Mutations were confirmed by DNA sequencing. Novel PALB2 alterations were analyzed for their potential effect on protein function or splicing using various in silico prediction tools. Three-hundred and seventy-two healthy controls were screened for the presence of the identified (potentially) functional mutations.

Results
A novel nonsense mutation, p.Y743*, was identified in one familial breast cancer patient (1/127, 0.8%). Besides, four in silico-predicted potentially functional mutations including three missense mutations and one 5’ untranslated region mutation were identified: p.D498Y, novel p.G644R, novel p.E744K, and novel c.-134_-133delTCinsGGGT. The mutations p.Y743* and p.D498Y were identified in two familial patients diagnosed with unilateral or synchronous bilateral breast cancer at the ages of 29 and 39, respectively. The other mutations were identified in an early-onset (≤ 30 years of age) breast cancer patient each. All five mutations were absent in 372 healthy controls suggesting that they are disease associated.

Conclusion
Our findings show that PALB2 mutations account for a small proportion of early-onset and hereditary breast/ovarian cancer cases in Pakistan.

Key words
Familial breast cancer, PALB2, Germ-line mutation, Pakistan

Introduction
Breast cancer has a substantial impact on the overall tumor burden in Pakistan comprising 40% of all female malignancies. In Pakistan, monoallelic germline mutations in the high- and moderate-penetrance breast cancer susceptibility genes BRCA1, BRCA2, TP53, CHEK2, and RAD51C account for approximately 25% of early-onset and familial breast cancer suggesting that other susceptibility gene(s) may be involved.

Recently identified PALB2 gene, a partner and localizer of BRCA2, acts as a link between BRCA2 and BRCA1 and enables DNA repair [1]. Biallelic mutations in PALB2 (FANCN) cause Fanconi anemia, with clinical features similar to those caused by biallelic mutations in BRCA2 (FANCD1) [2]. Monoallelic mutations in PALB2 confer susceptibility to breast cancer suggesting that PALB2 is another candidate to be a breast cancer susceptibility gene [3]. Deleterious PALB2 mutations are estimated to confer a 35% lifetime risk of breast cancer for the carriers [4].